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Haemodynamic and ADH responses to central blood volume shifts in cardiac-denervated humans

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Summary. Haemodynamic responses and antidiuretic hormone (ADH) were measured during body position changes designed to induce blood volume shifts in 10 cardiac transplant recipients to assess the contribution of cardiac and vascular volume receptors in the control of ADH secretion. Each subject underwent 15 min of a control period in the seated posture, then assumed a lying posture for 30 min at 6° head-down tilt (HDT) followed by 30 min of seated recovery. Venous blood samples and cardiac dimensions (echocardiography) were taken at 0 and 15 min before HDT, 5, 15 and 30 min of HDT, and 5, 15 and 30 min of seated recovery. Blood samples were analysed for haematocrit, plasma osmolality, plasma renin activity (PRA) and ADH. Resting plasma volume (PV) was measured by Evans blue dye and per cent changes in PV during posture changes were calculated from changes in haematocrit. Heart rate (HR) and blood pressure (BP) were recorded every 2 min. In the cardiac transplant subjects, mean HR decreased ($P<0{\cdot}05$) from 102 b.p.m. pre-HDT to 91 b.p.m. during HDT and returned to 101 b.p.m. in seated recovery while BP was slightly elevated ($P<0{\cdot}05$). PV was increased by 6·3% ($P<0{\cdot}05$) by the end of 30 min of HDT but returned to pre-HDT levels following seated recovery. Plasma osmolality was not altered by posture changes. Mean left ventricular end-diastolic volume increased ($P<0{\cdot}05$) from 90 ± 5 ml pre-HDT to 105 ± 4 ml during HDT and returned to 88 ± 5 ml in seated recovery. Plasma ADH was reduced by 28% ($P<0{\cdot}05$) by the end of HDT and returned to pre-HDT levels with seated recovery. PRA was also reduced by 28% ($P<0{\cdot}05$) with HDT. These responses were similar to those of six normal cardiac-innervated control subjects and one heart–lung recipient. Therefore, cardiac volume receptors are not the only mechanism for the control of ADH release during acute blood volume shifts in man.

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Introduction

During water immersion, sodium and water are excreted in large amounts and are accompanied by a reduction in plasma antidiuretic hormone (ADH) (Gauer *et al.*, 1970; Gauer & Henry, 1983). Horizontal and anti-orthostatic (head-down) bed rest also result in increased excretion of sodium and water (Nixon *et al.*, 1979) and decreased plasma renin activity (PRA), aldosterone and ADH (Epstein *et al.*, 1975a, b). However, the mechanism(s) associated with these fluid–electrolyte changes in man are not clear. According to the Henry–Gauer hypothesis (Gauer *et al.*, 1970; Gauer & Henry, 1983), the sudden shift in fluids from the legs and abdomen into the chest and head leads to stretch of low pressure receptors (located in the atrium and/or pulmonary circulation) as evidence of an increase in total circulating blood volume. The result is a decrease in plasma ADH release from the neurohypophysis and a consequent increase in sodium and water excretion. Most of the evidence supporting this hypothesis has come from studies using the dog (Gauer & Henry, 1976; Linden, 1976; Donald & Shepherd, 1978), where the receptors have been shown to be primarily located in the atrial wall and the ADH response to be abolished by vagotomy. Recently the importance of the proposed Henry–Gauer atrial receptors in control of ADH responses to acute blood volume shifts in man have been challenged by observations that vagotomized non-human primates exhibit significant diuresis during water immersion or volume expansion (Gilmore & Zucker, 1978a; Peterson & Jones, 1983).

It was the purpose of this study to extend the scope of these latter animal studies to man. Body position change (head-down tilt) was used to shift significant blood and body fluid volume to the head and thorax and stretch atrial and centrally located volume receptors in one heart–lung transplant and 10 cardiac transplant recipients and compare responses to normal-innervated subjects. It was hypothesized that if atrial receptors contribute significantly to the control of body fluid and electrolyte regulation through ADH inhibition or stimulation, then individuals with little or no atrial afferent output, i.e. partial or complete denervated hearts, should exhibit little or no reduction in ADH when exposed to such induced acute blood volume shifts.

Subjects and methods

Three groups of subjects volunteered to participate in this study:

(1) nine male and one female cardiac transplant recipients known to have partial atrial denervation by the surgical procedure;

(2) one male heart–lung transplant recipient known to have almost total atrial denervation and complete denervation of pulmonary low pressure receptors; and

(3) five male and one female normal subjects (no history of cardiac disease by history or physical examination) who served as controls.

Table 1. Subject descriptive data

Subject groups	*n*	Age (years)	Height (cm)	Weight (kg)
Controls	6	44 ± 4	175 ± 5	77·2 ± 8·5
Cardiac transplant	10	40 ± 3	180 ± 2	73·2 ± 2·5
Heart–lung transplant	1	41	185	71·8

All transplantation procedures were accomplished at the Stanford University School of Medicine under the supervision of Dr Norman Shumway and subjects were at least 1 year post surgery. Their descriptive data are presented in Table 1. Informed consent that included a detailed description of the nature of the experiment was obtained from each subject.

The subjects underwent exposure to and return from 6° head-down tilt (HDT) designed to induce cardiac volume changes by acute blood volume shifts. HDT was used because of its known effect to cause larger haemodynamic responses compared to horizontal posture (Tomaselli *et al.*, 1987). Each subject was instrumented in the supine position during an initial 30 min period to allow for the stabilization of a baseline physiological state. The experimental protocol is presented in Fig. 1. Following a 15 min control period (pre-HDT) in the seated position, each subject assumed the lying posture at HDT for 30 min, followed by a 30 min recovery consisting of a return to the upright seated position. The subjects were instructed to remain as motionless and relaxed as possible throughout the experiment.

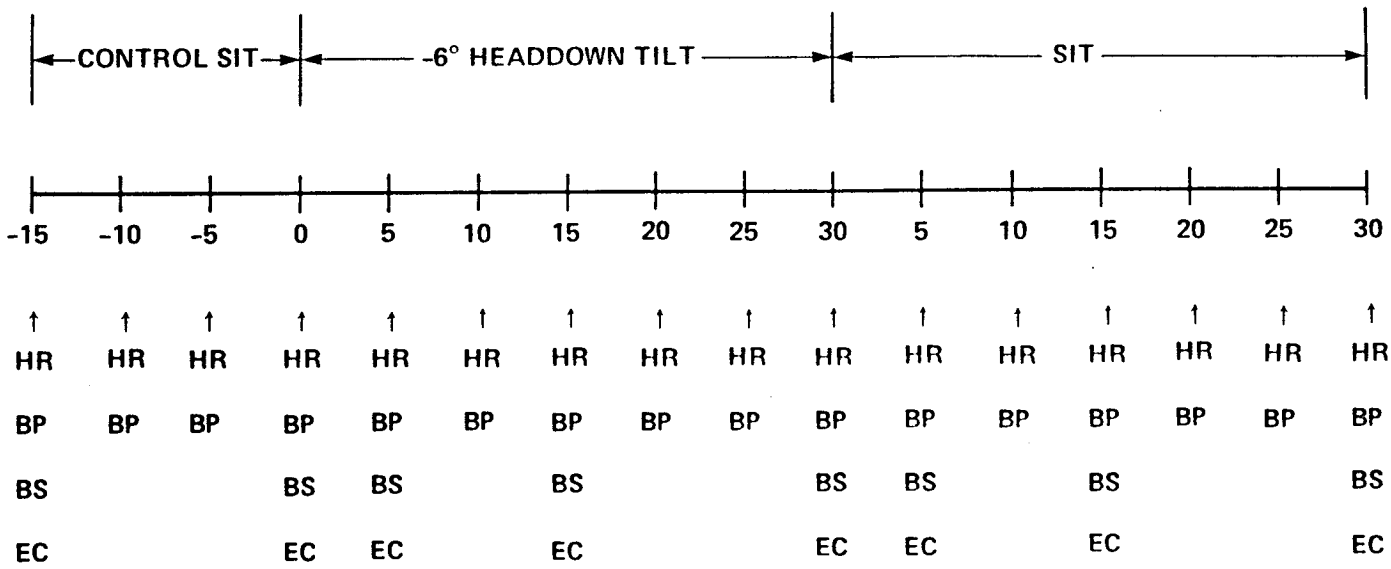

Fig. 1. Experimental protocol.

Just prior to the initial 15 min pre-HDT period, a 21-gauge needle with polyethylene catheter was inserted into the left arm antecubital vein and plasma volume (PV) was measured with a modified Evans blue dye dilution method (Greenleaf *et al.*, 1979). The patency of the catheter was maintained for the remainder of the experiment by occasional flushing with heparinized saline. Blood samples (10 ml) were collected without stasis at 0 and 15 min of pre-tilt, at 5 15 and 30 min of head-down tilt, and 5, 15 and 30 min during seated recovery. Duplicate microhaematocrit (Hct) determinations were made immediately after collection of each blood sample. The Hct samples were centrifuged for 12 min at 11 500 r.p.m. in a model MB International Centrifuge and read on an International Hct reader with a measurement error of ±0·25%. Raw haematocrit values were collected for whole-body Hct by multiplication with the factor 0·91 (Chaplin *et al.*, 1953). Per cent change in plasma volume from the initial seated control position was calculated from the corrected Hct values with the equation described by Greenleaf *et al.* (1979). The absolute change in plasma volume at any time during the protocol was calculated by multiplying the per cent change in PV by the measured PV.

Approximately 3 ml of blood was introduced into a glass tube containing lithium heparin, centrifuged at 1200 *g* for 15 min, and the plasma was analysed for osmolality by freezing point depression (Advanced Instruments, Needham Heights, Massachusetts). Approximately 5 ml of the blood sample was introduced into a pre-chilled vacuum-type collection tube containing ethylenediaminetetraacetic acid and centrifuged at 1200 *g* for 15 min at 4°C. From this sample, ADH concentration was determined using the sensitive radioimmunoassay technique described by Keil and Severs (1977), and PRA was analysed with the modified method of Haber *et al.* (1969) using a New England nuclear kit.

Heart rate (HR), systolic (SBP) and diastolic (DBP) blood pressures were measured every 2 min before, during and after tilt. Heart rate was counted from a 15 s strip-chart ECG recording (Hewlett-Packard, Waltham, Massachusetts). Right brachial blood pressures were measured manually with a calibrated sphygmomanometer and stethoscope. Diastolic pressure was recorded as the pressure at Korotkov-sound disappearance. Mean arterial pressure (MAP) was calculated by dividing the sum of SBP and twice DBP by 3.

A Hewlett-Packard ultrasonic echocardiography system (model 77020A) using *M*-mode scanning was used to determine an index of heart volume changes at 0 and 15 min of pre-tilt, 5, 15 and 30 min during head-down tilt, and 5, 15 and 30 min of seated recovery. Left ventricular dimensions were measured from the endocardial echo of the posterior left ventricular wall to the endocardial echo of the left side of the interventricular septum. Dimensions were recorded at the end of systole and diastole. These dimensions were used to compute end diastolic (EDV) and end-systolic (ESV) volumes using the Teichholz formula (Teichholz *et al.*, 1974). Stroke volume (SV) was determined as the difference between EDV and ESV. Cardiac output ($\dot{Q}$) was the computed product of HR and SV.

Results are presented as means ± SE. Since this study consisted of repeated measurements of each variable for different groups, changes within each group and across groups were evaluated statistically by using a two-way analysis of variance for repeated measures. The null hypothesis was rejected when $P<0{\cdot}05$ and non-significant differences were denoted by NS. Since there was only one heart–lung transplant subject, these data were not included in the statistical analysis. We have included the data separately as a descriptive comparison against the controls and heart-transplant subjects.

Results

Mean (± SE) haemodynamic and hormonal responses at the end of pre-HDT, HDT and seated recovery in the subject groups are presented in Table 2 and the mean time course of these responses is presented in Fig. 2. In the control subjects, EDV increased ($P<0{\cdot}05$) from pre-HDT to 30 min of HDT and returned following 30 min of seated recovery. The increase in EDV with HDT resulted in an increase ($P<0{\cdot}05$) in SV at 30 min of HDT with a return to pre-HDT levels at 30 min of seated recovery. $\dot{Q}$ increased ($P<0{\cdot}05$) with HDT despite a compensatory decrease ($P<0{\cdot}05$) in HR (Fig. 2). HR and $\dot{Q}$ returned to pre-HDT levels with 30 min of sitting recovery. Except for an initial elevation in SBP at 5 min of HDT ($P<0{\cdot}05$), SBP, DBP and MAP were not significantly altered during body position changes (Table 2 and Fig. 2). Compared to resting control values, plasma volume was significantly increased during HDT, but returned to control levels following seated recovery. HDT provoked a 37% reduction ($P<0{\cdot}05$) in plasma ADH levels (Table 2), which returned to control values upon resumption of the seated position during recovery. PRA was decreased slightly ($P<0{\cdot}05$) by HDT compared to pre-HDT and remained depressed during 15 min of the seated recovery period.

The cardiac transplant subjects had higher ($P<0{\cdot}05$) resting heart rates, blood pressures and PRA, and lower ($P<0{\cdot}05$) end-diastolic volume, stroke volume and circulating plasma volume compared to the control group (Table 2). However, haemodynamic responses to tilt in the cardiac transplants were similar (NS) to those measured in the controls (Table 2 and Fig. 2). For the transplant subjects, SBP was elevated ($P<0{\cdot}05$) during the initial 5 min of HDT, but returned to pre-tilt levels by 15 min HDT and was not altered thereafter. Diastolic and mean arterial pressures were not altered by body posture changes (Fig. 2). Plasma volume and EDV increased ($P<0{\cdot}05$) following 30 min of HDT and returned to pre-tilt levels at 30 min of sitting recovery. Similar to the response in the control subjects, EDV changes in the cardiac transplant subjects resulted in increased ($P<0{\cdot}05$) SV and $\dot{Q}$ at 30 min of tilt with a return to pre-HDT levels at 30 min of seated recovery (Table 2 and Fig. 2). Plasma ADH was reduced by 28% ($P<0{\cdot}05$) by 30 min of HDT and returned to control levels following resumption of the upright seated position (Table 2). PRA was reduced ($P<0{\cdot}05$) by 30 min of HDT and did not return to control levels during seated

Table 2. Haemodynamic and hormone responses at the end of sitting, 6° head-down tilt (HDT) and recovery sitting

Variables		Controls	Cardiac transplant	Heart–lung transplant
End-diastolic volume, ml			*	
15 min sit pre-HDT	A	114 ± 5	90 ± 5	86
30 min HDT	B	138 ± 5	105 ± 4	106
30 min sit recovery	A	112 ± 3	88 ± 5	83
End-systolic volume, ml				
15 min sit pre-HDT	A	47 ± 3	48 ± 3	41
30 min HDT	A	49 ± 4	49 ± 3	42
30 min sit recovery	A	47 ± 3	46 ± 3	41
Stroke volume, ml			*	
15 min sit pre-HDT	A	67 ± 4	42 ± 4	45
30 min HDT	B	89 ± 5	56 ± 4	54
30 min sit recovery	A	65 ± 5	43 ± 4	42
Heart rate, b.p.m.			*	
15 min sit pre-HDT	A	64 ± 3	102 ± 4	100
30 min HDT	B	59 ± 4	94 ± 4	97
30 min sit recovery	A	67 ± 4	101 ± 4	100
Cardiac output, l min^{-1}				
15 min sit pre-HDT	A	4·29 ± 0·35	4·26 ± 0·30	4·50
30 min HDT	B	5·25 ± 0·45	5·21 ± 0·39	5·24
30 min sit recovery	A	4·36 ± 0·25	4·18 ± 0·22	4·20
Systolic blood pressure, mmHg			*	
15 min sit pre-HDT	A	114 ± 4	130 ± 5	130
30 min HDT	A	115 ± 5	133 ± 8	130
30 min sit recovery	A	116 ± 6	131 ± 3	130
Diastolic blood pressure, mmHg			*	
15 min sit pre-HDT	A	80 ± 4	99 ± 3	90
30 min HDT	A	82 ± 4	103 ± 7	90
30 min sit recovery	A	79 ± 5	101 ± 2	95
Plasma volume, ml			*	
15 min sit pre-HDT	A	3316 ± 214	2926 ± 158	3167
30 min HDT	B	3521 ± 238	3120 ± 180	3475
30 min sit recovery	A	3223 ± 190	2904 ± 151	3167
Antidiuretic hormone, pg ml^{-1}				
15 min sit pre-HDT	A	3·0 ± 0·6	2·5 ± 0·8	5·6
30 min HDT	B	1·9 ± 0·7	1·8 ± 0·5	3·8
30 min sit recovery	A	3·2 ± 0·9	3·2 ± 1·0	5·8
Renin activity, ng Ang I ml^{-1} h^{-1}			*	
15 min sit pre-HDT	A	0·9 ± 0·1	1·8 ± 0·3	3·2
30 min HDT	B	0·4 ± 0·2	1·3 ± 0·5	2·0
30 min sit recovery	B	0·4 ± 0·1	1·3 ± 0·3	1·8

Values are means ± SE.

A, B: denotes significant ($P<0.05$) differences between stages; same letters are not different.

*$P<0.05$ control vs. cardiac transplant values.

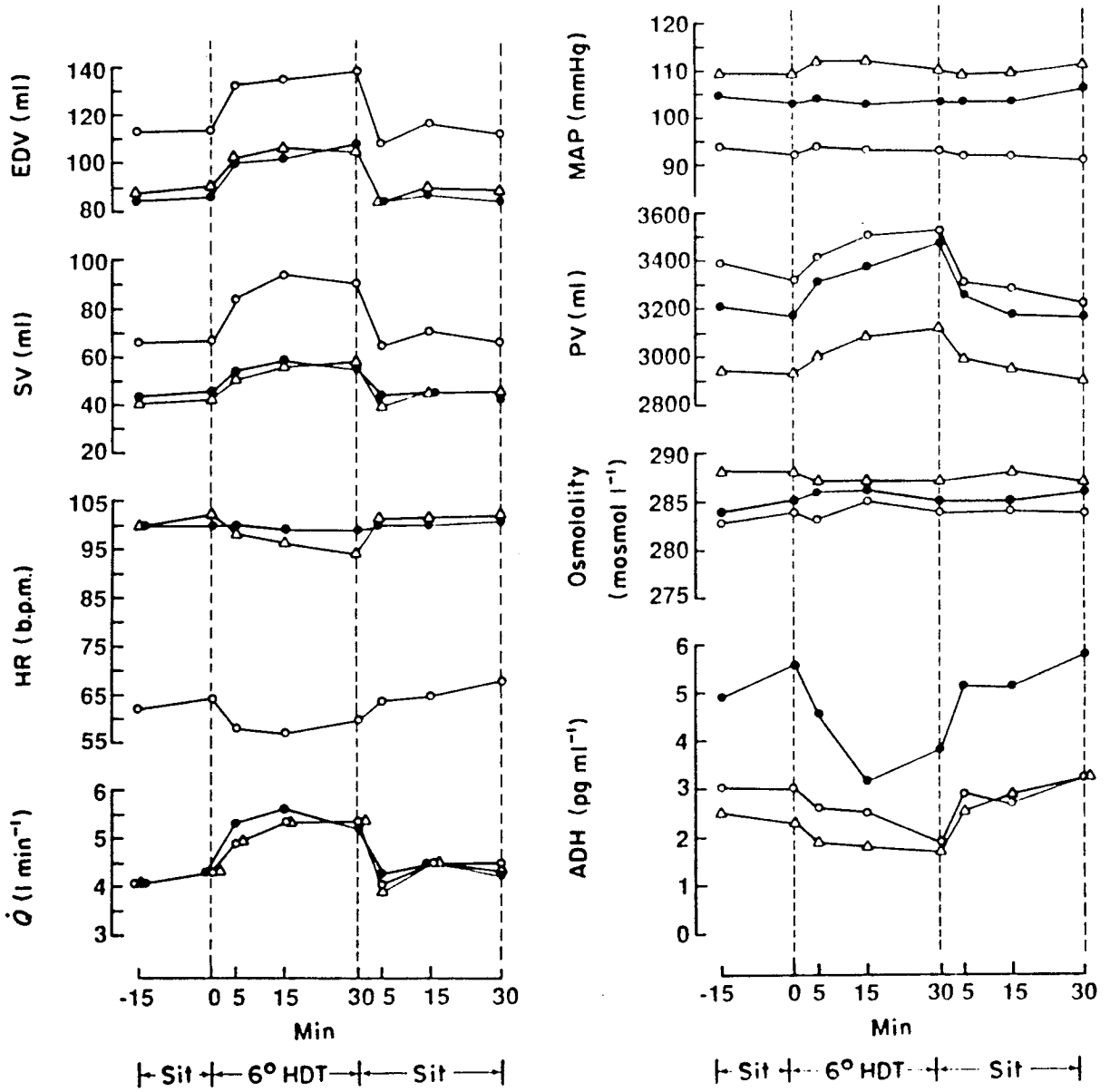

Fig. 2. Haemodynamic, plasma volume (PV), osmolality and antidiuretic hormone (ADH) responses before, during and after 6° head-down tilt in normal subjects (control ○), cardiac transplant subjects (△) and in a heart–lung transplant subject (●). Values are means.

recovery (Table 2). The one heart–lung transplant recipient demonstrated similar responses in plasma volume, ADH and PRA levels and haemodynamic adjustments to those measured in the cardiac transplant and control subjects (Table 2 and Fig. 2).

Initial resting plasma osmolalities of 288 ± 2 mosm l^{-1} in cardiac transplant subjects, 283 ± 3 mosm l^{-1} in controls and 284 in the heart–lung subject were not significantly altered during body position changes in any of the experimental groups throughout the protocol (Fig. 2).

Discussion

In the present study, 6° head-down tilt induced an acute headward shift of fluids sufficient to enlarge the heart volume in cardiac and heart–lung transplant, as well as normally innervated control subjects, as indicated by a significant 17% increase in echocardiographically measured left ventricular end-diastolic volume. These changes were associated with transient increases in plasma volume indicating shift of extravascular fluid to the circulation and a reduction in heart rate and insignificant changes in mean arterial pressures. All transplant and control subjects demonstrated a decrease in plasma PRA and ADH. These haemodynamic and ADH responses were reversed by 30 min of resumed sitting following head-down tilt. These data demonstrated that cardiac and heart–lung transplant recipients have mechanisms to alter ADH secretion during acute blood volume shifts.

The secretion of ADH can be affected by a number of possible stimuli including changes in plasma osmolality, the renin–angiotensin system, atrial natriuretic peptide, neurogenic factors, cardiopulmonary baroreflexes and/or arterial baroreflexes. Hyperosmolality can stimulate the release of ADH (Robertson, 1974; Robertson & Athar, 1976), but this mechanism appeared unlikely in this experiment since plasma osmolality was not altered during all posture changes. Plasma renin activity could be an indirect stimulus since angiotensin II stimulates ADH release (Ramsay *et al.*, 1978). However, in the present study, after reduction by head-down tilt, PRA did not return to pre-tilt levels following resumption of upright sitting, despite the return of ADH to resting levels. Although PRA has a considerably longer half-life than ADH, these data suggest that PRA changes were not related to changes in ADH.

Atrial natriuretic peptide (ANP) appears to influence plasma ADH in humans. Stimulation of ADH secretion following a rise in plasma osmolality can be inhibited by ANP infusions (Allen *et al.*, 1987), and, in a more relevant study, it has been shown that the ADH response to 2 h of head-up tilt was abolished by infusions of ANP during the tilt period (Williams *et al.*, 1988). Therefore, it is possible that ANP may also play an active role in the regulation of ADH in the response to posture changes in our transplant subjects.

Sympathetic nervous activity may stimulate the release of ADH (Chalmers & Lewis, 1951). Although not measured in our study, sympathetic nervous activity probably contributed very little to the responses of ADH since acute central volume shifts do not appear to alter significantly catecholamine levels (Stene *et al.*, 1980; Epstein *et al.*, 1983). However, our results suggest that a primary stimulus for the changes observed in plasma ADH induced by acute posture changes was directly associated with significant blood-volume shifts.

Considerable controversy exists as to whether the cardiopulmonary mechanoreceptors and/or the arterial baroreceptors are important in the regulation of ADH secretion in man. Although the role of atrial volume receptors in the control of ADH secretion has been demonstrated in dogs (Gauer *et al.*, 1970; Gauer & Henry, 1976,

1983), data from studies using the non-human primate have suggested that these receptors may play a small role in regulating blood volume. Similar increases in atrial pressure or stretch which induced a diuresis in the dog (Gauer & Henry, 1976; Linden, 1976; Fater *et al.*, 1982) failed to elicit any renal effects in either the anaesthetized or conscious monkey (Gilmore & Zucker, 1978b; Peterson *et al.*, 1980, 1983; Cornish & Gilmore, 1982). Furthermore, cervical vagotomy (Gilmore *et al.*, 1979) or complete, selective cardiac denervation (Peterson & Jones, 1983) failed to attenuate the diuretic response to volume expansion or water immersion in the monkey, although ADH levels were not measured in these animals. These species differences between dogs and primates raise a question about the role of cardiac receptors in the control of ADH secretion in man. The findings in this study parallel those observed in the vagotomized and cardiac-denervated non-human primate during blood-volume expansion.

The present study is unique in that plasma ADH levels were measured during blood-volume redistributions induced by body posture changes in humans with cardiac denervation. Since our preliminary results were first reported (Convertino *et al.*, 1984), Drieu *et al.* (1986) described responses of ADH secretion in cardiac transplant patients following a 10–12% plasma volume depletion induced by furosemide administration. Changes in PRA, heart rate and blood pressure observed in our cardiac transplant patients were similar to those observed in the Drieu transplant subjects. In contrast to our findings, they observed no change in ADH in transplant subjects compared to control subjects and concluded that cardiac receptors play a dominant role in ADH secretion in humans. These differences are possibly due to study design: receptors were unloaded in the Drieu study and loaded in our study. Responses may vary in these instances (Goetz *et al.*, 1975). In addition, the transplant patients in the Drieu study may have been slightly dehydrated at the time of study since they had baseline ADH levels which equalled that of control subjects after volume depletion, a condition which may have blunted the response in their transplant subjects.

In contrast to the findings of Drieu *et al.* (1986), i.e. that normal subjects demonstrated 145% increase in ADH with volume depletion, several investigators have reported that stimulation of cardiopulmonary mechanoreceptors by either haemorrhage (Goetz *et al.*, 1974; Robertson, 1983) or low levels of lower body negative pressure (Rogge & Moore, 1968; Goldsmith *et al.*, 1982) does not alter ADH levels in humans. Norsk *et al.* (1986a) demonstrated that ADH variations were weakly correlated ($r = -0{\cdot}39$) with central venous pressure alterations induced by expansion or reduction of blood volume during immersion. They concluded that cardiopulmonary mechanoreceptors are not of prime importance in the regulation of ADH in man. Our data are consistent with these and other previous observations (Rogge & Moore, 1968; Goetz *et al.*, 1974; Goldsmith *et al.*, 1982; Robertson, 1983; Norsk *et al.*, 1986a) and suggest that the control of ADH secretion in man may not be completely explained by cardiac mechanoreceptor reflexes since plasma ADH changes were similar in cardiac-denervated subjects during acute blood-volume shifts compared to controls.

Some caution in the interpretation of our data to indicate complete non-contribution of cardiopulmonary mechanoreceptors is provided by the knowledge that significant portions of the recipient atria may be left intact with heart transplantation (Reitz *et al.*, 1981). It might be argued that the similar ADH responses observed in the heart transplant recipients and the normal cardiac-innervated subjects may be partly explained by stimulation of residual atrial nerve endings which remain in the small atrial cuff of the recipient heart, since these areas are known to contain large numbers of atrial receptor sites (Linden, 1976). The functional capacity of this receptor area following transplantation is unknown. In all cases, transplant recipients included in this study endured severe and persistent evidence of congestive heart failure which formed a basis for their subsequent surgery. Atrial receptors had undergone prolonged periods of previous excessive stretch. To date there is no report or evidence of reinnervation of donor hearts (M. Billingham, personal communication). Furthermore, all subjects in the present study had been tested with regard to Valsalva response within the first 2 months of surgery and the expected negative heart rate response was present. Although our experiments were conducted at least 1 year later, functional tests of deep breathing and Valsalva manoeuver performed by cardiac transplant patients 4–93 months post operation confirmed that vagal denervation remained present (Drieu *et al.*, 1986). Suppression of vagal tone in our subjects was also suggested by their higher resting heart rate. Finally, during heart-lung transplantation only the superior–inferior vena cava junction and a small portion of the recipient right atrium are left intact resulting in removal of 80% or more of centrally located low pressure baroreceptors capable of contributing receptor input. Therefore, it is concluded that the role of any residual receptor area in explaining similar ADH responses between cardiac–denervated and control subjects was probably negligible since similar haemodynamic and ADH responses were observed in the heart–lung transplant recipient who represented complete cardiac denervation.

Our results and those of others (Robertson, 1983; Norsk *et al.*, 1986a, 1987) suggest that mechanisms other than cardiopulmonary mechanoreceptors in the control of ADH secretion in man should be considered. Reduction in arterial pressure provoked by haemorrhage combined with head-up tilt (Robertson, 1983), water immersion (Norsk *et al.*, 1986a), and termination of neck suction (Norsk *et al.*, 1987) is associated with elevated ADH levels while increased arterial pressure induced by graded water immersion decreased ADH (Norsk *et al.*, 1986b). These observations implicate an important role of high pressure baroreceptors in the response of ADH to blood-volume redistribution. Our data suggest such a mechanism was involved during head-down tilt in transplant subjects since an apparent arterial baroreflex response, i.e. elevated systolic blood pressure and lower heart rate, was associated with lower ADH levels. However, these possibilities will require further study.

Lastly, increased pressure within the cranial vault may play a role. The venous pressure is a determinant of cerebral spinal fluid drainage and increased venous pressure is likely within our protocol. Elevated intracranial pressure has been measured in monkeys during water immersion and 6° HDT (L.C. Keil, personal

communication). It is reasonable to suspect that an intracranial pressure-sensing system within the brain provides redundancy in the regulation of ADH release when information from peripheral input is impaired.

In conclusion, the results of the present study demonstrated that the responses of heart rate, stroke volume, cardiac output, arterial blood pressure, plasma volume, osmolality, plasma renin activity and antidiuretic hormone provoked by acute redistribution of blood volume, and cardiac filling induced by posture changes are similar in cardiac-denervated subjects compared to normal controls. These results suggest that cardiac and heart–lung transplant recipients have mechanisms by which blood volume can be regulated by altering plasma ADH levels. These data are consistent with the hypothesis that the control of ADH secretion during acute blood-volume shifts in man cannot be explained by the role of cardiac volume receptors alone and may suggest that atrial natriuretic peptide, arterial baroreflexes, and/or intracranial regulatory systems contribute to the regulation of ADH release.

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